WHAT IS CLAIMED IS:

1. A method of determining a level of activity of a protein in a cell type, comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to said protein, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to said protein represents said protein activity level in said cell type.

2. The method of claim 1 wherein protein activity levels are quantitated for each level of perturbation to said protein in said step of providing perturbation response profiles, and said quantitated protein activity levels are normalized to wild type protein activity levels so that the levels of perturbation may be expressed in units of percent-

protein activity, and wherein said determined protein activity level is thereby expressed as a percent-protein activity level.

3. The method of claim 2 wherein said protein activity levels are quantitated by performing a biological assay of a function of the protein.

4. The method of claim 2 wherein said protein activity levels are quantitated by measuring the level of abundance of said protein.

5. The method of claim 1 wherein said interpolating comprises approximating by a sum of spline functions.

6. The method of claim 1 wherein said interpolating comprises approximating by a Hill function.

7. The method of claim 1 wherein said determined level of perturbation is a level which minimizes the value of an objective function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for said determined level of perturbation.

8. The method of claim 7 wherein said objective function comprises a sum of the squares of differences of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

9. The method of claim 7 wherein said objective function comprises the negative of a correlation of said drug response and said model drug response.

10. The method of claim 1 wherein said cell type is substantially isogenic to *Saccharomyces cerevisiae*.

11. The method of claim 1 wherein said cell type is from a human.

12. The method of claim 11 wherein said protein is implicated in susceptibility or resistance to a disease or disorder.

13. The method of claim 1 wherein said first plurality of cellular constituents and said second plurality of cellular constituents comprise abundances of a plurality of RNA species present in said cell type.

14. The method of claim 13 wherein the abundances of said first plurality and said second plurality of RNA species are measured by a method comprising contacting a gene transcript array with RNA from a cell of said cell type, or with cDNA derived therefrom, wherein a gene transcript array comprises a surface with attached nucleic acids or nucleic acid mimics, said nucleic acids or nucleic acid mimics capable of hybridizing with said plurality of RNA species, or with cDNA derived therefrom.

15. The method of claim 14 wherein said measuring of said abundances of said second plurality of RNA species is performed by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from said cell of said cell type in which said protein activity is known or suspected to be perturbed, and (ii) with RNA, or with cDNA derived therefrom, from said cell of said cell type in which said protein activity is not perturbed.

16. The method of claim 13 wherein said first plurality of RNA species constitutes the majority of RNA species known to be increased or decreased in said cell type upon perturbation to said protein.

17. The method of claim 14 wherein said first plurality of RNA species constitutes the majority of RNA species known to be increased or decreased in said cell type upon perturbation to said protein.

18. The method of claim 1 wherein said cellular constituents comprise abundances of a plurality of protein species present in said cell type.

19. The method of claim 18 wherein the abundances of said plurality of protein species are measured by a method comprising contacting an antibody array with proteins from a cell of said cell type, wherein said antibody array comprises a surface with attached antibodies, said antibodies capable of binding with said plurality of protein species.

20. The method of claim 18 wherein the abundances of said plurality of protein species are measured by a method comprising performing two-dimensional electrophoresis of proteins from a cell of said cell type.

21. The method of claim 1 wherein said cellular constituents comprise activities of a plurality of protein species present in said cell type.

22. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising causing inducible expression of said

protein in said cell type under the control of a controllable recombinant expression system.

23. The method of claim 12 wherein said inducible expression is achieved in said cell type wherein endogenous expression is knocked out.

24. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising controllable transfecting of genes expressing said protein.

25. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising controllably decreasing abundances of RNA species encoding said one or more specific cellular constituents in a cell of said cell type.

26. The method of claim 25 wherein said method of controllably decreasing said abundances of RNA species comprises exposing a cell of said cell type to ribozymes targeted to cleave said RNA species.

27. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising controllably decreasing the rate of translation of RNA species encoding said one or more specific cellular constituents in a cell of said cell type.

28. The method of claim 27 wherein said method of controllably decreasing the rate of translation of RNA species comprises exposing a cell of said cell type to antisense nucleic acids or antisense nucleic acid mimics that

hybridize to said RNA species or to DNA encoding said RNA species.

29. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising controllably decreasing abundances of said protein in a cell of said cell type.

30. The method of claim 29 wherein said method of controllably decreasing said abundances of said protein comprises causing expression in a cell of said cell type of said one or more protein species as fusion proteins comprising said protein species and a degron, wherein said degron is controllable to increase the rate of degradation of said protein.

31. The method of claim 29 wherein said method of controllably decreasing said abundances comprises exposing a cell of said cell type to antibodies, wherein said antibodies bind said protein.

32. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising exposing a cell of said cell type to varying levels of one or more drugs which directly and specifically inhibit said activity levels of said protein.

33. The method of claim 1 wherein said plurality of discrete levels of perturbation to said protein is achieved by a method comprising exposing a cell of said cell type to varying levels of a dominant negative mutant protein species, wherein said dominant negative mutant protein species is a protein inhibiting said activity of said protein.

34. The method of claim 1 wherein said diagnostic profile is from a cell of said cell type that has been treated with a drug, and said protein is a target or suspected target of said drug.

35. A method of identifying a cell of a cell type, that has one or more genetic mutations or polymorphisms that disrupt activity of a corresponding gene product, comprising determining a level of perturbation to said gene product at which the similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to said gene product, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in said cell, wherein said perturbation response curves are the products of a method comprising

(i) providing perturbation response profiles of said gene product for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a wild type cell of said cell type at a plurality of discrete levels of perturbation to said gene product, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said gene product, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to said gene product represents the extent to which the activity of said gene product is disrupted, and wherein cells in which the determined gene product activity is disrupted are identified as having said genetic mutations or polymorphisms.

36. The method of claim 35 wherein said cell type is from a human.

37. A method of identifying an individual suspected of having one or more genetic mutations or polymorphisms that disrupt activity of a corresponding gene product, comprising identifying cells derived from the individual as having said genetic mutations or polymorphisms according to the method of claim 35.

38. The method of claim 37 wherein said individual is a human.

39. The method of claim 36 or 38 wherein said gene is implicated in susceptibility or resistance to a disease or disorder.

40. The method of claim 37 wherein said perturbation response profiles are obtained by a method comprising analyzing the expression profiles derived from individuals having said genetic mutations or polymorphisms, and comparing said expression profiles to analogous expression profiles derived from wild type individuals.

41. The method of claim 35 wherein the corresponding gene product is a protein.

42. The method of claim 35 wherein the genetic mutations or polymorphisms are heterozygous mutations or polymorphisms.

43. A method for measuring activity of a drug *in vivo* comprising determining an activity level of a protein in a cell treated with said drug according to a method comprising determining a level of perturbation to said protein at which

similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for the determined level of perturbation to said protein, wherein:

(a) the diagnostic profile is obtained by a method comprising measuring a first plurality of cellular constituents in the cell treated with said drug; and

(b) the perturbation response curves are provided by a method comprising

(i) providing perturbation response profiles of said protein for a cell, wherein said perturbation response profiles are obtained by a method comprising measuring a second plurality of cellular constituents in a cell at a plurality of discrete levels of perturbation to said protein,

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

and wherein said determined level of perturbation to said protein represents said protein activity level in said cell treated with said drug and said protein activity level is a measure of said drug activity.

44. The method of claim 43 wherein said drug increases the activity of said protein.

45. The method of claim 43 wherein said drug decreases the activity of said protein.

46. The method of claim 43 wherein said perturbation response profiles are calibrated to one or more clinical affects of said drug.

47. A method for determining the dose of one or more drugs to achieve a desired clinical effect in a patient comprising determining the dose of said one or more drugs so that similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a) the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said one or more drugs; and

(b) the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i) providing a plurality of perturbation response profiles of said one or more drugs for one or more cells of one or more patients, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells at a plurality of discrete levels of exposure to said one or more drugs, and

(ii) calibrating said plurality of perturbation response profiles to clinical effects of the one or more drugs.

48. The method of claim 47 wherein said method of providing the perturbation response profile associated with the desired clinical effect further comprises as step of interpolating said plurality of perturbation response profiles so that a

perturbation response profile may be extracted over a range of levels of perturbation to said protein.

49. A method for determining a drug therapy to achieve a desired clinical effect in a patient comprising determining the drug therapy so that similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein,

(a) the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said drug therapy; and

(b) the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i) providing a plurality of perturbation response profiles for a plurality of drug therapies, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells for a plurality of drug therapies, and

(ii) calibrating said plurality of perturbation response profiles to clinical effects of the plurality of drug therapies.

50. The method of claim 49 wherein said method of providing the perturbation response profile associated with the desired clinical effect further comprises as step of interpolating said plurality of perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein.

51. The method of claim 49 wherein said plurality of drug therapies comprise drug therapies wherein one or more drugs administered is varied.

52. The method of claim 49 wherein said plurality of drug therapies comprise drug therapies wherein the dosage of one or more drugs administered is varied.

53. A computer system for determining a level of protein activity comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to said protein, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to said protein represents said protein activity level in said cell type.

54. The computer system of claim 53 wherein determining the level of perturbation is achieved by a method comprising:

(a) determining the value of an objective function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b) minimizing said determined value of said objective function by varying the level of perturbation to said protein to determine a level of perturbation that minimizes said determined value of said objective function.

55. The computer system of claim 53 wherein said diagnostic profiles and said perturbation response curves are made available in said memory.

56. The computer system of claim 55 wherein said programs cause said processor to perform said step of interpolating said perturbation response profiles.

57. The computer system of claim 54 wherein said objective function comprises a sum of the squares of differences of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

58. The computer system of claim 54 wherein said objective function comprises the negative of the correlation of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

59. The computer system of claim 54 wherein said minimizing comprises performing the Levenberg-Marquandt method.

60. A kit for determining the level of activity of a protein in a cell type comprising a solid phase containing on its surface a plurality of nucleic acids of known, different sequences, each at a known location on said solid phase, each nucleic acid capable of hybridizing to an RNA species or cDNA species derived therefrom, said RNA species known to be increased or decreased in response to a perturbation to said protein in said cell type, said plurality substantially excluding nucleic acids capable of hybridizing to RNA species that are not increased or decreased in response to said perturbation.

61. A kit for determining the level of activity of a protein in a cell type comprising

(a) a solid phase containing on its surface a plurality of nucleic acids of known, different sequences, each at a known location on said solid phase, each nucleic acid capable of hybridizing to an RNA species or cDNA species derived therefrom, said RNA species known to be increased or decreased in response to a perturbation to said protein in said cell type; and

(b) perturbation response curves of said protein for said cell type, wherein said perturbation response curves are in electronic form, wherein said perturbation response curves are the product of a method comprising:

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a

plurality of discrete levels of perturbation to said protein; and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a continuous range of levels of perturbation to said protein

wherein said interpolated response profiles comprise said perturbation response curves.

62. The kit of claim 60 which further comprises, in electronic or written form, perturbation response curves of said protein for said cell type, wherein said perturbation response curves are the product of a method comprising :

(a) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(b) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein

wherein said interpolated response profiles comprise said perturbation response curves.

63. The kit of claim 61 or 62 wherein said perturbation response curves are in electronic form, and wherein said kit further comprises expression profile analysis software on computer readable medium, said software capable of being encoded in a memory of a computer also having a processor, said encoded software causing said processor to perform a method comprising:

(a) receiving a diagnostic profile of a cell of said cell type, said diagnostic profile having been obtained by a method comprising measuring abundances of RNA species or cDNA derived therefrom from said cell type. by a method comprising hybridizing said RNA or cDNA to said plurality of nucleic acids on the surface of said solid phase in a cell of said cell type;

(b) receiving said perturbation response curves; and

(c) determining the level of perturbation to said protein at which similarity is greatest between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves,

wherein said determined level of perturbation to said protein represents the level of protein activity.

64. A database comprising perturbation response curves for one or more proteins from one or more cell types wherein said database is in electronic form, wherein said perturbation response curves for each of said proteins for each of said cell types are the product of a method comprising:

(a) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(b) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a continuous range of levels of perturbation to said protein

wherein said interpolated response profiles comprise said perturbation response curves.

65. A method of determining a level of activity for each of one or more proteins in a cell type, comprising determining a level of perturbation to each said protein at which similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said protein for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, wherein said perturbation response curves for each of said proteins are the products of a method comprising

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves

wherein said determined level of perturbation to each said protein represents said activity level of each said protein in said cell type.

66. A method of identifying a cell of a cell type, that has one or more genetic mutations or polymorphisms that disrupt activity of one or more corresponding gene products, comprising determining a level of perturbation to each said gene product at which the similarity is greatest between a

diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said gene product for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in said cell, wherein said perturbation response curves for each said gene products are the products of a method comprising

(i) providing perturbation response profiles of said gene product for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a wild type cell of said cell type at a plurality of discrete levels of perturbation to said gene product, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said gene product, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to each said gene product represents the extent to which the activity of said gene product is disrupted, and wherein cells in which corresponding gene product activities are disrupted are identified as having genetic mutations or polymorphisms in said genes.

67. A computer system for determining levels of protein activity comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a

method comprising determining a level of perturbation to each said protein at which similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said protein for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, wherein said perturbation response curves for each of said proteins are the products of a method comprising

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves

wherein said determined level of perturbation to each said protein represents said activity level of each said protein in said cell type.

68. The computer system of claim 67 wherein said determining the level of perturbation is achieved by a method comprising:

(a) determining the value of an objective function of the difference between said diagnostic profile and the combination of the perturbation response profiles extracted from said perturbation response curves for said level of perturbation to each said protein; and

(b) minimizing said determined value of said objective function by varying the level of perturbation to each said protein to determine the level of perturbation to each said protein that minimizes said determined value of said objective function.